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EDITORIAL

A CALL TO CLINICIANS

MEDICAL and Veterinary knowledge is founded on the recorded observations and experiences of our forebears. It can be likened to a fountain which has been primed by the men of the past and can be kept at an ever-growing flow by those who follow.

Until the beginning of the 19th century, much of the information of which there is record was not based on original observation but was simply a re-hash of the philosophical meditations of the learned men of ancient times. It lost none of its romance in the telling. In those days it was a brave man who would contest the dictates of these great men. In the early part of the 19th century it is manifest that a change in thought and outlook was in being. In British Veterinary literature this change was momentous, and it can be counted as a landmark in the history of our profession. About this time energetic steps were being taken to place veterinary science, and particularly the training of the future surgeons, on a sound basic scientific background.

For a man who could show proficiency in the arts and crafts, the financial and other rewards were great. This attracted a number of very able and well-trained men to our ranks from the sister profession of medicine. It was a fortunate circumstance that many of these men, whilst they welcomed the enhanced reward, made strenuous efforts also to advance the status and scientific renown of their adopted profession, and they took steps to record their thoughts and observations for the benefit of others. They had not the information or a tithe of the scientific aids at hand which have become commonplace to-day, but they were astute observers and experimentalists of first degree. Any doubts on this score are quickly dispelled if one turns the pages of the early issues of the *Veterinarian*. Many of the papers and articles found therein would meet with approbation if they were presented to-day. Moreover, the composition is framed in delightful English and is a reflection of the culture of the writers and editors of those days. These early issues carried also a vigorous and informative correspondence section. And so things continued until the latter part of the 19th century, with the torch of clinical knowledge burning fiercely.

Then came a decline and even the cut and thrust of the correspondence columns lost much of its edge. For fifty years the scientists of the laboratory have held the field. No doubt this was a logical consequence of the reorientation of thought and outlook as those subjects with a laboratory background were incorporated into the curriculum. To these men, the publication of records of work and research became almost an obsession; indeed, advancement in their particular line became dependent upon the amount and volume of published work. It is not in any way our intention to decry or in any way damp the ardour of our men in the laboratories, for they have added much to the store of knowledge. Rather it is our object to urge our modern clinicians to emulate them.

The very foundations of veterinary science were well and truly laid by clinicians; there is much that they can do now, and the first and foremost requisite is that they record their observations for the benefit of their fellows. We would like to see in this Journal, and also in the columns of our contemporaries, a greater volume of material from the pens of those who work in the field.

Remember. If the clinicians were abolished, the profession would die.

GENERAL ARTICLES

RECENT DEVELOPMENTS IN IMMUNITY, MORE PARTICULARLY FROM THE STANDPOINT OF VETERINARY MEDICINE, AND WITH ESPECIAL REFERENCE TO EGYPTIAN CONDITIONS*

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(*Continued*)

The conversion of a strain of virus or other pathogen from "pantropism" to "neurotropism" does not exhaust by any means the prospects that are opening up in this direction.

Hitherto, in this section of our essay, stress has been given mainly to the advances made in immunisation procedure with the use of "live" immunogens, taking as our examples diseases caused by the filtrable viruses. It is probably in the case of those diseases that the advances worthy of special mention have been most dramatic. Much has been accomplished, however, in the case of bacterial diseases, and, in so far as they are of particular relevance to veterinary medicine, the examples of BCG vaccination against tuberculosis and vaccination with "Strain 19" against bovine contagious abortion (bovine brucellosis) are selected for brief description.

In the case of both these diseases—namely, tuberculosis and brucellosis—the immunity after recovery from infection differs from that following recovery from the virus diseases above specially mentioned. In the case of those virus diseases, recovery from natural infection or from a reaction following inoculation with an attenuated immunogen was followed by an immunity of long duration. In the case of foot-and-mouth disease, the immunity following recovery has been proved to be solid against infection with the homologous immunological type of virus for at least two years. In the case of cattle plague, where the existence of distinct "types" has not yet been definitely proved and the immunological problem in practice is consequently much simplified, the immunity produced similarly is much longer and probably usually lasts throughout the life of the animal.

In the case of both tuberculosis and brucellosis, on the other hand, there is available much evidence to suggest that an animal only possesses a specially high degree of resistance while it is actually a "carrier" of infection, and that when the animal body is completely rid of all traces of infection it soon becomes again susceptible to contracting disease in a severe form.

It was McFadyean who proved, in 1896, that cattle harbouring tuberculous lesions (as disclosed by the tuberculin test) but showing no clinical symptoms of tuberculosis were highly resistant to artificial infection with tubercle bacilli. After it had been proved by Koch, in 1901, that bovine tuberculosis and human pulmonary tuberculosis differed in etiology in so far as they were caused by types of tubercle bacilli showing well-defined biological variations, von Behring attempted to

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immunise cattle during calfhood by inoculating them intravenously with cultures of the "human type" of tubercle bacilli. Against this type, cattle have a very high degree of resistance, but after intravenous inoculation the bacilli can be proved to persist for several months in the lungs without setting up macroscopic lesions. During this time and for a short time afterwards, the resistance of the inoculated bovine towards infection with virulent tubercle bacilli of the "bovine type" could be shown to be considerably increased. That a useful degree of immunity could be set up in this way was confirmed by McFadyean and his colleagues in 1915, who, moreover, proved that a similar increased resistance could be set up in cattle against infection with the "bovine type" of tubercle bacilli by intravenous inoculation with the "avian type" of tubercle bacillus.

There were soon disclosed obvious difficulties in adopting the methods suggested in practice. Firstly, after inoculation with the milder "type" of tubercle bacillus, immunity did not become effective against infection with the more virulent type until a fairly long interval had passed, extending, it seemed, to three months. Only very rarely—namely, only when tuberculosis in the pregnant mother affects the placenta—does a calf born from a tuberculous mother show evidence of tuberculosis at birth. As to the immense majority, estimated to be the proportion of 500 to 1, when calves contract tuberculosis, it is contracted during extra-uterine life; but, in a highly infected environment, especially when sucking a mother excreting tubercle after birth, the calf might become contaminated so early that it would be impossible to intervene early enough with immunisation to set up protection.

The only possible way to secure any benefit from the immunisation would be to take the calf away from its mother immediately after birth, place it in strict segregation, in company only with other known healthy calves, until the estimated age when it could best withstand immunisation and benefit from it—namely, when it had reached an age, perhaps of 3 to 6 months—and afterwards take great care to ensure that it did not become exposed to massive infection with tuberculosis for another three months or so.

In spite of the difficulties, it was a rationale of the above kind that formed the basis of the system, advocated particularly by Bang in Denmark, for building up tubercle-free herds from herds that, on the evidence of repeated examination by means of the tuberculin test, were known to be free of tuberculosis. No immunisation procedure was recommended, but reliance was placed upon the tuberculin test to detect "carriers" of infection. The testing was carried out at regular intervals until a clean herd, composed of non-reactors and calves weaned away from infected mothers at birth and kept free from exposure to infection, was gradually built up to replace the diseased herd. The much later procedure, adopted with conspicuous and complete success in the U.S.A., where such a drastic procedure was economically practicable on account of the relatively low general incidence (about 10 per cent.) of tuberculosis among cattle there, as compared with the high general incidence in Western Europe (about 40 per cent.), which would render a similar procedure economically prohibitive as a State undertaking, has been to slaughter off at once all reactors disclosed at successive tuberculin

tests, until the herd is "accredited" clean, and compensate the owners liberally for the destruction of their animals.

It has been necessary to introduce the above statement which has no direct bearing on immunity, though it has immense significance in preventive medicine, because there are clearly several areas in the world where "sanitary police" or "stamping-out" methods cannot be applied to control tuberculosis, but in these particular areas, if a satisfactory method of immunisation were known, it would be worth attempting.

Concurrently with the above progress in evolving methods of control, the French workers Calmette and Guérin, at the Pasteur Institute, had been occupied in modifying the virulence of the "bovine type" of tubercle bacillus itself. The method which they adopted was to cultivate it repeatedly on glycerinated potato which was soaked in bile, apparently to render its conditions of growth unfavourable by lowering the surface tension upon it. After a very long series of transfers in this way, they managed to secure such a well-marked change in the virulence of the organism that, after subcutaneous inoculation, cattle showed only slight local lesions and no macroscopic generalised disease.

Eventually, in classic researches which they carried out clandestinely in the course of the First World War during the German occupation of Northern France, at the Pasteur Institute, Lille, they were able to prove definitely that calves which had been inoculated with their "bile-treated" bacillus, BCG (i.e. Bacillus of Calmette and Guérin), were completely or nearly completely resistant to natural infection, in the shape of close continuous contact in a cowshed with cows known to be highly tuberculous and to be discharging tubercle bacilli in their excreta. The same preliminary considerations naturally governed as in the case of the von Behring method using the "human type" of tubercle bacillus—namely, that after immunisation an adequate interval had to elapse before the calves were exposed to infection.

It had been Calmette's view, deduced from his own researches on the subject, that natural infection in tuberculosis was commonly by way of the mouth and not by inhalation. The bacillus of tuberculosis being essentially pneumotropic, after ingestion in small doses and traversing the intestinal wall and afterwards the barrier represented by the mesenteric glands, eventually established itself in the lungs and bronchial and mediastinal lymphatic glands. This view, however, has been strenuously controverted by other workers, who claim to have proved that pulmonary tuberculosis can be set up with minimal doses of tubercle bacilli by inhalation, whereas massive doses are required to produce infection by ingestion, and then, when infection succeeds, lesions of tuberculosis are always to be seen in the intestines and mesenteric glands.

Acting upon the assumption, however, that in tuberculosis the common path of invasion was along the alimentary route, Calmette believed that immunisation with BCG could be achieved by administering the cultured bacilli by the mouth. In France, until the time of his death, the method was exploited a good deal, both in human beings (to protect against the "human type," for BCG was also believed to be protective against it) and in calves. Elsewhere, the results reported have

been varied; in Canada, for example, the researches of Watson would seem to show that the method was unsatisfactory. The disasters which happened in Lübeck, in Germany, among children who had been accidentally administered virulent tubercle cultures instead of BCG, as was discovered on later enquiry, most unfortunately delivered a serious setback to progress in obtaining experience in the use of the method and effecting improvements.

Tuberculosis has long been known to be a disease widely distributed among the animal kingdom. Besides the three classic "types"—human, bovine and avian—there are also known to exist types which affect cold-blooded animals, such as fishes, and some attempts have been made, without success, to use these organisms in immunisation against infection in warm-blooded animals. While investigating the natural causes of the ebb and flow in numbers of the smaller rodent populations, workers (Wells *et al.*) under the animal ecologist, Elton, at the Bureau of Animal Populations, Oxford, discovered that at least one of the causes for sharp decline among field voles (*Microtus agrestis*) was widespread tuberculosis. The tubercle bacillus isolated from the lesions, however, differed from the above three classic types known to infect warm-blooded animals. In particular, after inoculation into bovines subcutaneously it produced local lesions with little or no tendency towards generalisation, and after intravenous inoculation it produced merely latent infection, as with the "human type" and BCG, and little or no evidence of any macroscopic lesions. From such researches as have been subsequently reported—work having been suspended largely during the late war—the vole bacillus appears to be superior to BCG in the immunisation of cattle against the "bovine type" of bacillus. It appears able to establish itself more firmly in the tissues and protection is obtained with greater regularity and certainty.

While dwelling on this theme of tuberculosis immunisation, mention must be made of the method devised by Vallée and Rinjard for conferring an immunity upon cattle against Johne's disease. In France, at any rate, it appears to have given in field practice some quite encouraging results. What the precise conditions are for infection in this curious disease are at present very imperfectly understood. From the researches of Hagan and his colleagues, particularly in the U.S.A., it would seem possible that the infection can only be contracted by the very young, in which afterwards it may or may not establish itself, to produce much later the characteristic chronic and insidious enteritis after an incubation period which may extend to two years. In some respects, it bears a close resemblance to human leprosy, which is also caused by an organism of the acid-fast group, with a selective affinity for the skin and subcutaneous tissues. Adult cattle cannot be readily infected by any known means, at least to produce disease with the characteristic symptoms. To protect cattle against the onset of the clinical disease, Vallée and Rinjard conceived the idea of inoculating them subcutaneously with live cultures of the Johne bacillus, and, to prevent rapid elimination from the site of inoculation, to suspend the cultured bacilli in a menstruum composed of vaseline. The vaseline hindered absorption and a long persisting, small swelling remained at the site of

inoculation. This would appear to be about the first attempt recorded to promote delay in absorption in this way. Again, conditions imposed by the late war have retarded acquisition of satisfactory information upon the real value of the method.

Since the discovery of the common cause of contagious abortion in cattle by Bang in Denmark in 1896, as the organism which is now known as *Brucella abortus*, an immense amount of work has been done to devise measures for the control of this disease, which to livestock owners in Western countries is probably economically the most serious infectious disease confronting them. On the whole, the measures devised have been, for one reason or another, unsatisfactory. Whereas, for example, in the U.S.A. eradication of bovine tuberculosis by elimination of carriers, as disclosed by the tuberculin test, was carried through to a triumphant conclusion, even with the great monetary wealth of that country behind it, on the other hand a scheme put in motion to eradicate bovine contagious abortion by the elimination of carriers as disclosed by the application of the agglutination test upon the blood serum of cattle signally failed. It seems to be far more difficult to ensure satisfactory conditions of segregation with brucellosis than with tuberculosis, and the task of identifying actual carriers with certainty seems also to be more difficult.

Immunisation against the disease has also suffered a chequered history. In Stockman's early researches, evidence seemed to be forthcoming that while killed cultures of *Brucella abortus* had no immunogenic value, the inoculation of massive doses of live cultures subcutaneously, when given a short time before conception, enabled a pregnant cow to carry her calf to full term even when exposed to infection causing a high rate of abortion in her immediate neighbourhood.

The field evidence in support of this system was, however, somewhat disquieting. It was not always easy to undertake the controlled observations necessary to obtain unequivocal information, especially when such observations were forthcoming only from private practitioners untutored in the methods of assessing scientific information. Bovine brucellosis was well known to be a self-limiting disease in which, depending mainly on the virulence of the infecting organism and partly also probably upon the genetic susceptibility of the cow, infection was followed by all gradations in morbidity. The morbidity varied from a state in which, in its most chronic form, the cow remained a persistent carrier, without ever showing overt abortion, to states in ascending order of virulency in which the calf was born alive but premature or, again, the cow aborted once only and then calved normally; or, again, in exceptionally severe form, to states in which cows aborted twice or even three times in succession, but afterwards always tended to revert to clinically normal calving, even though they remained persistent carriers.

In such conditions, it would be fatally easy to ascribe to a vaccine the disappearance of clinical abortion which would, in any case, have taken place if it had not been used.

In some instances, again, practitioners reported very unfavourable sequelæ following the use of the vaccine, such as persistent sterility, which could not be satisfactorily explained.

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For a time, therefore, vaccination was generally abandoned in favour of elimination through systematic application of the agglutination test, though some workers, both in England (McEwen) and America (Schroeder and Cotton), persisted in efforts to devise better means of vaccination. Meanwhile, in its turn, as already stated, elimination through application of the agglutination test came to suffer serious eclipse.

Much light came to be thrown upon the properties of strains of *Brucella abortus* depending upon their colonial "roughness" (R) or "smoothness" (S) on solid culture media, CO_2 sensitivity, and capacity for establishing themselves in the tissues (chief among which was the mammary tissue) of non-pregnant animals without wandering afterwards, when the uterus became gravid, to infect destructively the cotyledonary tissue. One of the strains that came for examination by the American workers (Strain 19) appeared to them to possess the desired properties in remarkable degree, and steps were taken to ensure that these properties were not lost, so that subcultures on an extensive scale could be issued to field workers for immunisation.

A further circumstance long revealed to workers in the course of research upon this disease was that, whereas adult animals which were proved to harbour infection as disclosed by agglutination testing remained persistent carriers of infection, very young reacting cattle almost invariably, at subsequent tests, disclosed evidence of having thrown off infection. This capacity to throw off infection declined as they increased in age until, when they reached about two years in age, it was no longer retained. The capacity to throw off infection would therefore appear to come to an end at the time when genital tissue, including accessory-genital tissue such as the mammary tissue, became capable of functioning. It had been abundantly proved that in the non-pregnant heifer and cow the main location of *Br. abortus* in which it remained in a state of arrested growth was the mammary tissue. Elsewhere in the body its hold on the tissues was insecure.

Hence, by selecting a suitable strain for vaccination and performing the vaccination at such an early stage in the animal's lifetime that the risks of permanent serious establishment were minimised, it was hoped that a successful method of vaccination for use in the field had been devised.

Calfhood vaccination with Strain 19 has now been adopted on an enormous scale in Britain as well as in America. Judging from the scale with which it is being propagated under very close State control, the experience already gained must be very highly in its favour, at least, in the ordinary epidemiological circumstances relating to the natural infection in Western countries, where, on the whole, the outbreaks prevailing are themselves caused by strains of a rather low grade of virulence. For, at any rate, the protection afforded, as disclosed by the weak results of tests in which vaccinated guinea-pigs are afterwards inoculated with challenging doses of virulent strains, cannot be of a very high level. In the matter of safeguarding the food supply of peoples—in particular milk and milk products—during the present critical times, the method however must be regarded in the light of a considerable boon to humanity.

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The Interference Phenomenon in Active Immunity produced by Live Immunogens

Pasteur's classic researches from 1881 to 1888 produced the means of preventive treatment for rabies for which, to most people, his name will be best remembered. The mode of action of the treatment has, however, remained almost completely a mystery to the immunologist. Indeed, to the highly critical, some doubt has always lingered in the mind in regard to the actual validity of the treatment. The reports of Pasteur Institutes throughout the world giving figures which would purport to display the striking degree of protection afforded to treated persons bitten by dogs affected with, or suspected to be affected with, rabies, have not escaped being viewed with some degree of scepticism. For obvious reasons, treatment of persons at none of the Institutes could be carried out in the manner of a controlled experiment. Until very recently, with rapid improvement in methods of working upon virus diseases generally, the evidence to be derived from laboratory experiment upon animals had not been unequivocal. Almost invariably in all text-book descriptions, while the system of treatment recommended by Pasteur himself and all important later modifications have been more or less faithfully outlined, the question as to how and why the treatment works has been shirked. The impression would be gained that it was a system of treatment ventured upon by Pasteur empirically and that in the outcome he was extremely fortunate. Close inspection of Pasteur's original writings, however, by a practised worker soon dissipates that illusion, for the essential deductions from close and prolonged observation of his experimental subjects are there soundly drawn and fall into line with the revelations brought forth from different classes of immunological inquiry during the last few years. In short, the steps in Pasteur's original treatment are the following:

(a) A person is admitted for treatment who has just been bitten by a dog suffering from rabies.

(b) After a lapse of time which may extend from a few days to a few months, the person bitten would ordinarily risk developing rabies. The degree of risk would depend upon the severity of the bite, the concentration of virus in the dog's saliva, and the prospects of the virus reaching the central nervous system through the tissues.

(c) Vaccination, as hitherto generally understood, has been looked upon as a procedure which increases the resistance of the vaccinated individual to an infection, and that increased resistance, it has also been understood, must of necessity be set up *before* the action of infection. The increase in resistance, however, takes time, it has been thought, to develop. How long that may be in the case of the methods of vaccination adopted to protect against several known diseases has been already mentioned.

(d) The vaccine treatment of rabies, however, takes place perforce some time *after* the infection has been introduced into the body, and if this infection is to produce disease later in the spinal cord the infective agent, which in rabies is a virus, it must either have already established itself in the tissues or be lying dormant somewhere in the body.

(e) The vaccine used by Pasteur is a live immunogen, which is of the same kind as the "street virus" introduced by the dog bite but which has been modified considerably by adaptation to a species other than the dog—namely, the rabbit. That methods of securing "attenuation" in virulence have already been discussed fully. For the dog the virus has become a "weak" virus, very rarely producing death after inoculation under the skin, and the chances of its producing death, in Pasteur's own view, seem to diminish in proportion as the dose is increased. Dogs which had been inoculated in this way—that is, with the virus "fixed" for the rabbit—were afterwards found to be immune against inoculation with the natural (or "street") dog virus, even when this virus was introduced direct into the brain. On inquiry, by experiment, as to the time that must elapse before the protection of his dogs following inoculation with the "weak" rabbit virus (his *virus fixe*) became effective, he found that it could be shortened until it coincided with the moment of introduction of his "street virus" under the skin, and, indeed, the "weak" virus could be given with good effect for some time after the "street virus" was introduced. It is this point in Pasteur's original researches relating to his preliminary animal experiments that for about 60 years came to be overlooked. The point, in its general bearing on immunity problems, has only recently received confirmation, from observations which have usually been made quite haphazard and only rarely of set purpose—as, for example, by Pfaff in the case of cattle plague immunisation, in the manner of his particular experiments described already. Where Pasteur was exceedingly fortunate was that his grave fears in risking the application of the above information that had been obtained experimentally upon dogs to the treatment of his first human patient proved, in the event, groundless. For it might well have happened otherwise, in the light of our present far greater knowledge upon the properties of the viruses, and that first human being turn out to prove more akin to the rabbit than to the dog in the matter of susceptibility to a rabies virus adjusted in its affinities to the one or to the other of these two animal species.

(f) As a matter of caution, however, in the systematic treatment of bitten human beings, Pasteur devised a scheme whereby his patients were inoculated with a quick succession of large doses of increasingly active "fixed" rabbit virus. Decrease in activity, or viability, of the virus was obtained by progressive drying of infected rabbit spinal cords over solid caustic potash, and the first inoculation was performed with cord material estimated to have become completely inactive, by prolonging the drying to 14 days. In grave emergency, however, as when patients were badly bitten on the neck and face, and the "street" virus was expected to reach the brain within a few days, treatment was begun by actually risking the inoculation with a cord which had been dried for only one day, and in which, presumably, a very large proportion of the virus remained in a fully active state. The risk proved to be justified.

It is no part of our purpose within the space customarily alloted to an essay to deal with the modifications introduced later in the Pasteurian treatment, including those in which inactivated vaccine only was used in the treatment.

Confirmation of the above phenomenon has now been amply forthcoming from several sources:

First, workers upon plant virus infections (such as McKinney, 1929, and Thung, 1931, in the case of the tobacco mosaic virus; and Salaman, 1933, in the case of a virus disease of potatoes) came to observe a kindred phenomenon in which infection with a "weak" strain of virus blocked out simultaneous infection with a "strong" (i.e. highly virulent) strain of the same virus. Later, this was found to apply to human and animal virus infections. For example, Hoskins, in 1935 in America, observed that monkeys inoculated with the mouse neurotropic strain of yellow fever virus were protected against the lethal effects of the pantropic strain inoculated simultaneously with, or even shortly before, it. Magrassi (1935), in Italy, observed similarly that rabbits could be protected against an encephalitic strain of herpes virus by simultaneous inoculation with a non-encephalitic strain. Similarly, Findlay and McCollum (1937) showed that monkeys could be protected against virulent pantropic yellow fever by simultaneous inoculation with the milder Rift Valley fever virus; and Dalldorf, Douglas and Robinson (1938) showed that Rhesus monkeys could be protected against fatal infection with human poliomyelitis by simultaneous inoculation with dog distemper virus, which had been found to be infective for monkeys of this species but to cause only a low mortality.

Secondly, a striking exhibition of the phenomenon has been observed in the case of the bacteriophages, which are now generally accepted as of identical nature with the viruses. If, for example, a broth culture of *Bacillus coli* is first acted upon by a "weak" coli-phage, it will afterwards be resistant to a "strong" phage which would otherwise have produced prompt lysis. The question of the interval necessary for the bacterium after contact with the weaker phage to become resistant to the stronger one being then investigated, it was found that the two phages could be introduced simultaneously in a mixture and no lysis would take place. The weaker phage therefore, by gaining its foothold on the bacterial wall, would have prevented the incursion of the stronger one.

Thirdly, besides what has now been mentioned here as confirmatory of the phenomenon in the case of cattle plague, the researches of R. G. Green in America upon the virus of dog distemper have proved that with a ferret-adapted strain, which has lost its lethal action for dogs, protective immunisation can operate even when the adapted strain is inoculated simultaneously with the virulent original dog distemper virus. Furthermore, provided the symptoms of distemper are not too far advanced, the adapted strain after inoculation into dogs showing the early stages of severe clinical symptoms will quickly bring about abatement of these symptoms, followed by recovery. A new system of treatment in infectious disease, based on immunological principles, thus opens up. (It was noteworthy that at least the case of one field worker [Diferawi Bey, chief inspector, Upper Egypt], in the early course of the recent epidemic of cattle plague in Egypt, recourse was had by him to inoculation of cattle with goat virus during an actual outbreak in a herd as a method found in his experience to stem the progress of the disease.)

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The phenomenon under review has been variously named, but is now generally known as the Interference Phenomenon. From the work of Northrop, it would appear that the viruses in their initial action upon the host cells closely resemble the digestive enzymes—that is, act in the manner of catalysts by becoming first adsorbed on to the surface of the protein nodules. Thereafter, depending upon the combination affected, the molecule may suffer no change in the case of a "weak" one, or "lytic disintegration" in the case of a "strong" one. If all available surface is first occupied by the weaker one, then catalysis is inhibited. With the advent of the electron microscope into laboratory use, ocular demonstration of the above is to be obtained in the case of bacteriophages.

The advance made in our appreciation of this particular immunological mechanism cannot but portend important developments in the mode of dealing with several infectious diseases in the future.

Much light has recently been thrown on what appears to be a closely related, if not identical, phenomenon, mainly through the work of Burnet and his colleagues in Australia upon the human influenza viruses. These viruses can multiply freely in the cell lining the allantoic cavity of the chick embryo, being present in very high concentration in the allantoic fluid two days after infection. This fluid is then found to possess the property, even when highly diluted, of agglutinating red blood corpuscles (fowl or human) in suspension. The reaction clearly follows adsorption of the virus to the surface of the red cells, the clumping being essentially due to "bridging" by virus particles adsorbed to adjacent cells. After a few hours at 37° C., the agglutination disappears or becomes much weaker, and the adsorbed virus is then found to have become liberated again into the suspending fluid. On testing the treated cells again with fresh virus after washing them, no agglutination occurs.

The virus would seem therefore to have acted like an enzyme in destroying the substance ("receptors") on the red cell surface to which it had been initially adsorbed. There are agents also which have since been discovered that can remove the cell surface "receptors" that allow agglutination by the influenza viruses. These agents comprise in prominent degree culture filtrates of two bacteria—namely, the anærobic bacterium of gas gangrene (*Clostridium welchii*) and the cholera vibrio. If, for example, a suitable culture filtrate of the latter organism is allowed to act on a 1 per cent. suspension of red cells for 30 minutes at 37° C., then addition of influenza virus fails to produce agglutination. The active agent in the cholera vibrio filtrate possesses the properties of a typical enzyme in so far as it is non-dialysable, precipitable by half saturated ammonium sulphate, is antigenic and is not used up in the course of its reaction with red cells.

The *receptor-destroying enzyme* ("RDE") can further be shown to act upon the surfaces of body cells other than red cells. In current laboratory research upon the influenza viruses the mouse is commonly used as a test animal, the virus suspension being introduced into direct contact with the cells lining the respiratory tract by intranasal instillation. Now it has been shown (Fazekas) that if a healthy mouse lung is excised and suspended in a suitable saline solution in a way that, by modifying the pressure on this solution inspiratory and expiratory movements

are continued in the lung and virus is then introduced into the lung through a cannula attached to the trachea, the whole of the virus becomes absorbed within five minutes, by the cells lining the respiratory tract. If, however, the lung is first treated with "RDE" and then washed out with saline before testing with virus, no virus whatever is absorbed. Again, if, on the other hand, the untreated lung is first allowed to absorb virus, and "RDE" then added, there is rapid and complete liberation of virus.

Likewise, it has been found (Stone) that when chick embryo is inoculated with influenza virus "RDE" is capable not only of preventing absorption of virus, but also of *protecting* the embryo against *infection* by even large (1.000) doses of virus.

These experiments would indicate that (as stated by Hirst) a necessary part in the initiation of infection of any body cell is union with, and destruction of, some special component of the cell surface. This component has now been discovered to be a mucin identical with, or similar to, the mucin secreted by various mucous glands, but differing from the mucin characteristic of the synovial fluid of joints and found in the connective tissues generally. Various preparations of glandular mucin are actively inhibitory to the influenza virus, but this inhibitory effect is removed by treating the mucin beforehand with "RDE."

It has been known for several years that many bacteria are aided in their invasive action upon tissues in virtue of their secreting a "spreading factor," i.e., of a factor which enables them or their products to permeate the tissues readily. This "factor" was proved to act specifically against the characteristic mucin of connective tissue, hyaluronic acid, and to be enzymatic in nature, i.e., hyaluronidases. The cholera vibrio happens to be the most potent of all the bacteria, which, however, attacks mucous *surfaces*. It secretes two different enzymes acting on different aspects of glandular mucin, namely: (a) a depolymerising mucinase, and (b) "RDE." These enzymes would seem likely to play a part in the initiation or extension of infection in the bowel analogous to the hyaluridonases in *Cl. welchii* or streptococcus infections of the connective tissue.

The influenza viruses would therefore possess as the only indispensable enzyme in their surfaces one which will allow penetration through the mucin molecules which form a protective layer of the exposed surface of the respiratory cells.

The film of mucin which normally covers healthy mucous surfaces may therefore serve as a protective screen on which viruses like the influenza virus can be adsorbed, and diverted at least temporarily from susceptible cells. The sole function of the mucin would therefore not be to act merely as a mechanical and cleansing agent.

It is clear that these very recent advances in our knowledge upon the nature of the protective mechanisms against infection present in the body are likely in the near future to provide us with considerable further light upon the nature of immunity processes and still newer methods of immunisation.

Genetic and Environmental Factors in Immunity

It would seem at first sight that very little of what has been said in the foregoing pages applies to the Plant Kingdom. And yet the study of immunity among plants is both of great interest in so far as it has contributed to our general understanding of the problem and of the greatest possible economic importance in so far as a proper understanding of it enables us to conserve the food supplies of man as well as of animals. For while products in the shape of sera and vaccines, the manufacture of which in the minds of many people has been assumed, quite wrongly, to be almost synonymous with immunology so far as it relates to man and animals, have no place in the pursuit of that study where plants are concerned, yet immense pains have been devoted in other ways to promote growth and maturation in plants from knowledge derived from a proper study of the subject, and those ways are certainly of great interest and often not inapplicable to the maintenance of well-being in animals and sometimes even in man. Conspicuous examples in the Plant Kingdom of the measures that have long assumed widespread importance bearing more or less directly upon the subject of immunity are the breeding of "rust resistant" strains of wheat and the importation into infected localities for sowing there of "seed" potatoes grown in environments where they are not prone to attack by the virus diseases that hinder propagation and eventually reduce the yield of tubers to an uneconomic level in the infected localities. The difference between the "immune" and the "infected" locality in the case of the latter example resides in the absence of the virus-transmitting plant biting fly from the "immune" locality and its presence in the "infected" locality.

Almost countless examples could be drawn from the Animal Kingdom to illustrate parallel differences between one locality and another depending upon the presence or absence of vectors that have the capacity to transmit certain infectious diseases.

Many other factors relating to the environment have, however, now been revealed to influence the onset of disease. In much the same way as they also concern the health of plants, these factors comprise those most intimately associated with climate (temperature, solar radiation, humidity), food supply (which in so far as the food of animals is concerned is mainly connected with the local soil characteristics), and, in a way and to a degree that have not yet been sufficiently well appreciated, the local animal and plant ecology. All these factors in their fluctuating relationship to each other may influence so much the occurrence and severity of infection as well as the resistance of the animal towards infection that one finds several diseases have a regional and a seasonal distribution. Animals having a high degree of resistance against the prevalent infections of a given region are said to be well "acclimatised" for that region. Obviously, acclimatisation, in this sense, means far more than a capacity to withstand well the climate of the region. This subject of "acclimatisation," with particular reference to immunity against certain diseases and also susceptibility towards certain diseases, is such an extensive one and one as yet so imperfectly understood in all its bearings

that, perhaps, in the present state of our knowledge, its significance can best be made clear by giving a few illustrative examples :—

(a) *Bovine Theileriasis* (*"Egyptian Fever"*).—The name "Egyptian Fever" is a misnomer, because in the Old World theileriasis is one of the most widespread infections among cattle within a latitude range comprising the tropical and sub-tropical zones. The limitation of the infection to those zones is now well known to coincide with the distribution of certain ticks that are able to live only at the temperatures prevailing in those zones. These are "dropping off" ticks, or "discontinuous feeders" (Rhipicephalus and Amblyomma spp.) in which the hæmosporidian parasites belonging to the genus Theileria undergo a certain short stage in their life cycle in which conjugation takes place between the gametes ingested in the blood sucked by the ticks into their stomachs while attached to an infected bovine. On becoming attached during a succeeding stage to a healthy bovine, the fertilised gamont is injected into the blood, to undergo an agamogonous phase of multiplication in the lymphocytic tissue wherever that tissue is found in the body followed by a gamogonous phase in the blood. It is the intensity of the agamogonous phase that determines pathogenicity, varying from that of the deadly epidemic type of infection which occurs sometimes in Southern Africa ("East Coast fever") to the very mild infection, rarely manifested by clinical symptoms, with which almost all cattle become infected in the tropical and sub-tropical regions of the Old World, and of which they become lifelong carriers. There are probably several immunological variants of the parasites, and various names have been given, probably unnecessarily, to the parasites, depending partly upon the intensity of the disease they set up and their immunological characteristics.

It would be very difficult to exaggerate the importance of this infection in so far as it acts as a deterrent against the "acclimatisation" of cattle imported from temperate zones into sub-tropical or tropical zones.

Within the endemic area, almost all cattle become infected during very early life, probably within the first few days after birth. At that stage they possess a relatively very high degree of resistance against the development of serious disease after infection and recover after usually showing only an occult or inapparent form of affection. Exceptionally, however, as in some parts of East Africa, the losses may be quite severe ("Amakkebe" type of infection). In any case, after passing through the effects of this initial infection, the indigenous cattle are afterwards resistant towards attack manifested by clinical symptoms, exceptions being when their state of "premunity" breaks down from some causes which are not clearly understood or the cattle encounter infection with an immunologically different variant of Theileria.

Cattle that have passed calfhood and are imported from "clean" countries, such as from England to India, or countries where the prevalent Theileria infection is of another "type," such as from South Africa to India, are, however, liable to succumb very soon to fatal theileriasis. In India a massive experience has been obtained to prove the disastrous effects of importing pedigree European cattle in an attempt to "improve" or "grade-up" the indigenous cattle, as the result of

their contracting this infection. There can be little doubt but that experience would also apply to Egypt.

(b) *Helminthiasis.*—To an extent that can hardly be realised by anyone who is not well versed in the subject, this is the cause of enormous loss among agricultural livestock in almost all countries, and particularly those in which conditions of temperature and humidity and overcrowding of animals upon pastures favour the development of those stages of the helminth parasites which need to be passed in the outside world. Where a stage or stages of the parasites need to be passed in one or more intermediate hosts, the problem assumes an ecological aspect. Bovine and ovine fascioliasis, for example, is related to the prevalence of certain species of freshwater snails in the vicinity of the susceptible hosts.

In the foregoing pages it has been stressed that, contrary to the popular view, a bad nutritional state is unfavourable towards the establishment of virus infections, fairly generally, and bacterial infections, in several instances, in the susceptible hosts, particularly when the infectious agent possesses a low grade of virulence.

It is otherwise almost universally with helminth infestations. There is now forthcoming most abundant proof that in several of these infestations, and particularly in those caused by the nematodes, the intensity of the clinical affection and the worm burden carried by the host are related to the state of nutrition of the host, being most severe and heaviest in animals which, from inadequate food supply, are in a *poor* state of nutrition.

Moreover, contrary to what occurs with the virus infections fairly generally and with a few bacterial infections (such as brucellosis), the susceptibility of the host to helminth infestation is most marked at an early age, declining afterwards during adolescence, until, when maturity is reached, the host becomes relatively highly resistant and may become a dangerous " carrier " towards the young without itself showing any symptoms. An apparently parallel phenomenon of varying age susceptibility is also displayed in the case of the coccidioses (see later).

Knowledge of this relationship between host susceptibility on the one hand, in its relation to age and nutritional state of the host, and intensity of infestation, on the other hand, depending both upon the characteristics of the environment which favour propagation of the worm parasites in it and upon the presence of " carriers " lies at the root of devising proper methods of control. For although great progress has been made within recent years in discovering medicaments with good anthelminthic properties, the application of these remedies alone is not of much benefit very often if measures are not concurrently adopted to keep the risks of recurring parasitic infestation under check. Thus, for example, in human ankylostomiasis, it has often been found of more benefit to the patient to treat his anæmia than to proceed to destroy the hookworms harboured by him, for, provided his body defences are restored, he is likely, without resort to specific treatment, to eliminate the parasites.

(c) *Mineral and " Trace Element " Deficiencies.*—Several diseases among the domesticated animals are now well known to be directly caused by these deficiencies, or, at any rate, to be intimately associated with them. Thus, for example, rickets

and osteomalaca are related to a calcium or phosphorous deficiency or imbalance, in the diet; "milk fever" in cattle is related to a low calcium level in the blood; "grass tetany" in cattle and "transit tetany" in horses are related to a low magnesium level; anæmia in young pigs, manifested by symptoms of depraved appetite (earth eating, etc.) is related to a deficiency of iron in the diet; "sway back" in lambs (endemic cerebro-spinal demyelinisation) is related to faulty assimilation of copper; and a widespread unthriftiness among cattle and sheep variously known as "bush sickness" in Australia and "pine" in sheep in Scotland is caused by a very low concentration of cobalt in the soil leading to a deficiency in the herbage. Excess of fluorine or molybdenum have again been proved to render some soils unhealthy.

Besides the direct effects, the widespread deficiency in the soils of extensive areas of the world in the above elements profoundly affects their susceptibility to disease. Thus, for example, in the "pine" districts of Scotland and the North of England, it is the highly increased worm burden that comes to be carried by the sheep as the result of the unthriftiness caused by the cobalt deficiency that leads mainly to the extensive losses among these animals. In India, on the other hand, it has been shown (Edwards) that the seasonal incidence of outbreaks of foot-and-mouth disease (a virus disease) is related to the fluctuating state of nutrition of the cattle, in the opposite direction, the disease appearing in epidemic form during "cold weather" months of the year when natural herbage becomes plentiful and the state of nutrition of the cattle is consequently good, and almost completely disappearing again when the hot weather comes round, and the land becomes parched, and the cattle fall away so much in condition that probably some millions die every year during this season from starvation. This last striking example of the contrary effects of nutrition is, of course, not one related mainly to mineral deficiency.

Instances of this kind can now be multiplied almost without number. A very curious relationship, however, was discovered some years ago in South Africa (Theiler, Green *et al.*) between the endemic incidence of an infectious disease in cattle, namely, a parabotulism, known locally as Lamziekte, and actual mineral deficiency in the soil. On the Lamziekte areas of the veldt the cattle were observed to exhibit a depraved appetite, their craving leading them to consume the carrion strewn on the veldt in the shape of the carcasses of dead animals. On bacteriological examination it was found that the symptoms of Lamziekte were produced by the ingestion of the toxins of a parabotulinus organism which invaded the carcass from the soils of those particular areas of veldt. The depraved appetite, however, of the cattle which resorted to eating these carcasses was caused by a very well-marked deficiency in phosphorous of the soil, and consequently of the herbage, on these areas of veldt. The feeding of the cattle with supplementary bone meal to remedy the phosphorous deficiency caused the disappearance of Lamziekte from the areas.

This discovery led to an important general economic finding, namely, that rather generally in South Africa the soils were deficient in phosphorous, and that

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supplementary bone-meal feeding brought about a very marked general improvement in the livestock of the country. The falling away in vigour of imported pedigree European breeds after two or three generations in the country could also in this way be largely remedied. It was hoped, therefore, that this knowledge would enable stock raisers to turn to breeding the more productive European breeds rather than continue to depend on the relatively unproductive Afrikander cattle. Careful experiments in acclimatisation were therefore carried out (Bischop) comparing the productivity and vigour of several imported European pedigree breeds of cattle with the local Afrikander cattle under South African conditions, over successive generations, giving them mineral supplements not only to make up for the striking local deficiency but also fully adequate supplements of all other minerals believed to be necessary. In spite of the most careful attention to this kind of supplementation and to the requirements of good husbandry, the imported breeds gradually fell away in productivity and vigour, while the Afrikander cattle, in the controlled experiments, kept under the same circumstances, fully retained their qualities.

This experience would fall into line with what had been previously experienced in India, namely, that imported European breeds, such as Ayrshires, Shorthorns, Jerseys and Holsteins, failed to grade-up satisfactorily the indigenous breeds on crossing with them, and that much the best livestock policy for the country was selective breeding from the local stock.

These lessons cannot be without significance to Egypt.

(d) *Cæcal Coccidiosis in Fowls.*—That variation in susceptibility alone caused by differences in age do not necessarily entirely account for the apparently greater resistance of adults than the young towards a given ubiquitous protozoan infection within an endemic area is illustrated by Horton-Smith's (1947) researches upon the epidemiology of coccidiosis among fowls. In England and several other countries, fowls become infected within the first few days of life almost invariably by the ingestion of ripe oocysts, which, in the case of those of *Eimeria tenella*, produce lesions of cæcal coccidiosis, followed by a mortality rate that depends upon a number of factors classifiable most appropriately as *ecological*. Among these factors are the atmospheric relative humidity, which is unfavourable to sporulation of the oocysts unless it remains near the saturation point in their immediate vicinity, and also the magnitude of the dose of oocysts ingested, which will depend largely upon the degree of crowding in the vicinity of affected birds and carriers. If the dose ingested is large enough to produce a powerful state of premunity but not so large as to cause death, the infected chick remains resistant against further infection. It is possible, however, to rear chicks free from infection by taking strict precautions to ensure isolation. In Horton-Smith's researches a group of 30 cockerels, for example, which had been reared free of coccidial infection until they had reached six months of age, was infected by giving a single sporulated oocyst to one of the birds. Within five weeks the whole group had succumbed to acute cæcal coccidiosis. The resistance of experimental chickens to fatal cæcal coccidiosis in later life was again found to be proportional to the magnitude of the

dose which survivors from an earlier artificial infection had received. By inhibiting mass extrusion of merozoites in the bowel wall after a heavy artificial infection through adequate dosing with sulphamezathine four days after infection, i.e., on the day before the development ordinarily of acute clinical symptoms, it was possible to save all the birds from death, which took place otherwise in 75 per cent. of the controls. The treated birds were afterwards all found to be completely resistant against massive infection. It would be obviously impossible to employ similar measures for immunisation or, more accurately, "premunisation" in field practice. Hence, what is recommended is that all birds in the immediate vicinity of any that are dying from coccidiosis should be at once administered one of the sulphonamide drugs found to be active against this infection, namely, sulphadiazine, sulphamezathine or sulphapyrazine, on the assumption that the infection has already obtained a foothold in them.

"A study of the epidemioligy of cæcal coccidiosis," Horton-Smith says, "shows very clearly that it is undesirable to maintain chicks free from infection: the aim should rather be one of controlling the intake of oocysts so that the birds are constantly picking up small doses throughout life. Coccidiosis in chickens provides an excellent example of the group of diseases caused by parasites of ubiquitous distribution. In this group of disease it is preferable to maintain the resistance of the host group by permitting an ever-present low-grade infection than to endeavour to prevent infection and thereby to retain the susceptibility of the host group."

Genetic Causes of Differences in Immunity

Already a good deal has been said in this essay in regard to differences in susceptibility of different races of cattle towards cattle plague. Differences of this kind have long been reported in the case of other diseases, such as the relatively high resistance of Algerian sheep towards sheep-pox and of Breton cattle towards anthrax. Among the general public there has always been a tendency to ascribe to hereditary influences the onset of certain diseases. This tendency, however, received a rude setback after the advent of the Pasteurian era, when the true and only cause of a very great variety of infectious diseases was proved to be invasion of the body with specific micro-organisms.

Tuberculosis is a case in point. Even before Robert Koch's discovery of the tubercle bacillus in 1882 there had been evidence to show that the disease could be transmitted artificially by the inoculation of animals with morbid material derived from tuberculous subjects. The view was, however, deeply ingrained in the minds of medical practitioners as well as the public that the disease arose through a hereditary "diathesis." Again, after the discovery, the same view was firmly held for long so much in the minds of the same class of people that research workers who had made themselves intimate with the pathogenicity of the tubercle bacillus were at great gains to discount entirely the importance of hereditary transmission, at least in comparison with the overwhelming importance of the specific infection with the bacillus, that is, of contagion. It was pointed out, for

example, as proof of the unimportance of heredity, that calves born from tuberculous mothers were almost invariably free from tuberculosis, and further that if care was taken to exclude risks of contagion they could be reared throughout life entirely free from tuberculosis. There was other abundant testimony to support the same view; and, with a subject the mysteries of which can only become commonplace and familiar to the practising bacteriologist, the specific role of the tubercle bacillus can never be overstressed in the ears of the public. That public, we well know, is made only too readily credulous of any ill-founded theory relating to disease. Especially is it prone to display credulity when that disease prevails as does tuberculosis as a deadly scourge among that public, with not a very great deal yet to point out in the way of achievement, certainly in the matter of "cure," as the outcome of precise knowledge upon etiology.

However, at last, there are signs that there is no longer any need to relate the role of the tubercle bacillus in the etiology of tuberculosis by overstressing it. The time seems to have arrived when proper enquiry can be made upon any factors, including genetic ones, that affect the host-pathogen relationship in this disease. The studies already made are not numerous, but they are illuminating.

Shortly before the first World War, Glen Liston and Soparkar, working in Bombay, reported experiments on a small scale which suggested that the Zebu cattle (*Bos indicus*) of India displayed a much higher resistance against artificial infection with the bovine type of tubercle bacilli than cattle of European breeds (*Bos taurus*). Under Edwards's direction, Soparkar continued these experiments afterwards on a large scale at Muktesar comparing the resistance of several of the Indian breeds of *Bos indicus* with that of European breeds. The conclusion was unequivocal that *Bos indicus* was far more highly resistant than *Bos taurus*. Moreover, contrary to the impression generally prevailing that tuberculosis was a rare disease among cattle in India, it was found to be actually widespread and common. The lesions which were produced in the indigenous cattle, however, differed greatly from those so very commonly seen in European cattle, inasmuch as invariably they remained very limited in size and restricted in distribution, mere "skin-lesion" and "no-lesion" tuberculosis being very common. It was not therefore that tuberculosis was a rare disease among cattle in India but that the cattle of the country were relatively highly resistant.

This work was later confirmed by Carmichael in Uganda. There, two distinct races of cattle are kept, namely, a Zebu type, as in India, and an old local breed of *Bos taurus* known as the Ankole breed. The latter breed, although it is never exposed to massive infection through being housed, but lives entirely in the open, was found to harbour, in very large proportion, lesions of tuberculosis, which tended to assume a widespread distribution in the body and become extensive in size. The Zebu type, on the other hand, though kept in closer domestication, rarely showed lesions, and even when found they tended to be very small and restricted in distribution in the body. Experimental work then clearly showed that the Ankole breed was much more susceptible than the Zebus. This confirmed the above Indian experience.

Among the smaller laboratory animals of a given species, again, it has more

recently been found possible by means of selective breeding to produce highly susceptible or highly resistant strains at will. Wells, for example, recently in America, for his work on aerial transmission of infection, bred selectively a strain of rabbits the progeny of which ultimately became so highly susceptible that a macroscopic spreading centre of infection was set up always in the lungs pointing to the site of every single tubercle bacillus inhaled.

It has now become an interesting question whether the selective improvement of the present well-known British and Dutch breeds of pedigree cattle that was begun in the latter part of the 18th century and has been continued assiduously since that time has been made without paying any regard whatever to disease resistance, in the endeavour made to concentrate on productivity only.

Much could be added upon what is now being reported upon this aspect of the problem of immunity. At present, the position is somewhat confused for want of enough reliable data. With the somewhat tardy interest taken by State authorities in sponsorship of genetic studies, there has been a delay in obtaining adequate information.

Conclusion

This essay, which has been written, around the title designated, at the express request of the examiners appointed by the University as part of a contribution submitted for a Degree Examination in the Faculty of Science, is recognised to have the serious limitations of this form of composition in general, the essay being, in the words of Samuel Johnson, merely "a random sally of the mind." It has not even the form and format of a modern scientific review, systematically written, with proper lists of references appended, which, in any case, could only have now been properly written upon a very small aspect of the whole subject of immunology.

The subject itself in its scope has now become immense. Since Kraus and Levaditi edited their standard two-volume treatise upon it over 40 years ago, the amount of relevant recorded information that could be summarised similarly has expanded well over twenty-fold. That does not mean to say that the enunciation of fundamental principles has increased by any means to a similar extent since the days of the great pioneers, Pasteur and Ehrlich. From a perusal of the writings of modern authors on the subject whose own experience has been also necessarily limited and often widely different from that of the author of the present essay and has been gained by them either in different localities or almost entirely within institutions, and not in the field, it is appreciated that this essay could have been written from very many standpoints that are different from the standpoint taken here. It is, however, but a "sally," as it is demanded to be, and it attempts to give in original an impression of a fringe of the subject from the somewhat unusual standpoint of Veterinary Medicine, especially as relevant to Egypt. Help from outside is gratefully acknowledged, in particular that given freely by the late Honorary Dean of the School of Veterinary Medicine, Fouad I University, Dr. J. T. Edwards.

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STUDIES ON EQUINE PURPURA HÆMORRHAGICA
Article No.2—*SYMPTOMATOLOGY*

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Introduction

THIS paper is the second in the series of reports submitted from the Royal Veterinary College, which are a result of a preliminary investigation into purpura hæmorrhagica undertaken early in 1947. It is based principally on the clinical records of three cases of purpura, all of which received hæmatological and biochemical examination. A brief history of a fourth case is included, because this animal was subsequently examined at post-mortem.

The purpose of publishing these case records is, first, to enable the reader to evaluate the degree to which the cases studied were typical of purpura. Secondly, and more especially, the intention is to enable correlation of the clinical symptoms with the hæmatological and biochemical abnormalities, details of which will be published in a later paper.

We would like to express our regret that, owing to the difficult circumstances which existed at the time, this, the clinical aspect of the inquiry into purpura, had to be undertaken without the co-operation of the clinical departments of the College.

General Account of the Influenza Epizootic, and of the Purpura Hæmorrhagica Outbreak which followed, in the L.M.S. Stables, London

Influenza was first diagnosed at the L.M.S. stables at the end of December, 1946. During the next few weeks the disease spread rapidly, not only in the L.M.S. stables, but throughout London generally. Eventually over 900 cases occurred among the L.M.S. horses.

The great majority of these cases were treated with sulphonamides and, on the average, were back at work in approximately 10 days. The remainder, 75 in number, received symptomatic treatment only and returned to work after an average period of over two weeks.

Purpura appeared in 10 horses, all of which happened to be derived from the group which received sulphonamide therapy; all were heavy draught horses. The fate of these 10 horses was as follows: five cases were given either formalin injections, or blood transfusions, or anti-histamine substances; four of these animals died and one recovered: of the five which were left untreated, two died and three recovered.

Material

Six out of the 10 horses which contracted purpura were examined during the course of this investigation. For the sake of convenience they were individually allocated the letters B, C, D, E, F and G.* Horses B and C were

* Horse A died before a clinical examination could be made. Furthermore, the animal was dismembered and some of the parts lost before arrangements could be made to conduct a proper post-mortem examination. In consequence, the observations made on this case were somewhat unreliable and were subsequently rejected.

examined both before and after death. B died within 12 hours of the start of the investigation and consequently afforded but little information. C, however, survived for three weeks, during which time blood and urine samples were taken, as nearly as possible daily, for hæmatological and biochemical examination. D and E both died before any clinical inspection could be made and were therefore only of interest from the point of view of morbid anatomy and histology. F was a mild case which recovered after eight days; blood and urine samples were examined, however, in the same way as for C. G died after the illness had run a severe course for eight days; hæmatological examination alone was undertaken. To summarise, the cases of B, C, F and G are of clinical interest and receive further consideration in this paper. It is important to add that horse B alone received treatment of any sort; the case of horse B, however, is only of minor importance.

Blood samples were taken from the jugular vein by the usual methods in quantities of approximately 150 ml. Urine samples were obtained from horses C and F only, both of which animals were mares. The method of digital pressure in the urethra was used to induce micturition, the degree of fullness of the bladder being checked by rectal examination. The dates on which blood and urine samples were obtained will be indicated in the later papers of this series, which report the results of the hæmatological and biochemical examinations.

Clinical Records

Horse B

Gelding, aged about five to six years.

After about 14 days' illness the animal died. It was examined clinically 12 hours before death. The following observations were recorded at this time:

Date	Pulse/ min.	Resp./ min.	Rect. temp.	
1.2.47	43	14	100.5	Slight œdematous swellings of the pectoral and groin regions. Large intermaxillary abscess, probably involving the submaxillary lymph node; this had been receiving treatment. General condition very weak.

Horse C

Mare, aged eight years.

Purpura first diagnosed on February 1, 1947.

Date	Pulse/ min.	Resp./ min.	Rect. temp.	
1.2.47	44	9	102.0	Slight œdematous swelling in intermaxillary space and anterior pectoral region. Difficulty in walking. Petechiæ on nasal mucous membrane and diffuse redness in conjunctiva. General condition good.
2.2.47	50	9	103.2	Increased swelling of intermaxillary and pectoral regions. Great swelling in anterior femoral and anterior tibial regions on both sides, with pain on palpation. Nasal mucous membrane very injected. General condition unchanged.

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3.2.47	84	13	105.0	Pectoral swelling extending now to xiphoid region. Femoral swelling spreading medially to the groin. General condition deteriorating.
4.2.47	80	12	104.0	Leg swelling now increased so as to involve the entire tibial region. No other change in the œdema. General condition very weak.
5.2.47	60	7	102.0	Œdematous swelling in all affected areas becoming reduced. Nasal mucous membrane less injected. General condition still very weak.
6.2.47	58	8	100.5	Further reduction in swellings. Nasal mucous membrane again injected. General condition still very weak.
7.2.47	62	10	101.0	Muscular tremors over most of body. Œdema unchanged. General condition still unchanged.
8.2.47	75	13	103.0	Appearance of new œdematous swelling of upper lip and nostrils on right side. Muscular tremors no longer present. General condition still unchanged.
9.2.47	70	6	102.0	Animal discovered down in the morning; parts of head bruised, causing closure of left eye. Œdematous swelling of anterior femoral region again conspicuous. General condition still unchanged.
11.2.47	76	9	103.5	No change.
12.2.47	80	12	101.3	Upper lip and nostril now swollen on left side as well as on right. Renewed swelling of intermaxillary space. Gulping occurring at regular intervals of several minutes. General condition still very weak.
13.2.47	84	6	102.0	Nostril swelling further increased on both sides. Otherwise no change.
14.2.47	62	10	102.0	No change.
15.2.47		No record		No change.
17.2.47	69	9	101.0	Distinct œdematous plaque (four inches in diameter and three-quarters of an inch high) appeared on left side of neck. General condition improved.
18.2.47	80	9	101.5	No change.
20.2.47	103	13	104.0	Plaque on neck regressing. Marked deterioration in general condition.

21.2.47	78	No record		General condition once again improved, but still weak. Slaughtered for post-mortem examination.

Horse F

Mare, aged five years.

Purpura first diagnosed on February 4, 1947.

Date	Pulse/ min.	Resp./ min.	Rect. temp.	
4.2.47	60	13	101.5	Œdematous swelling of both hind legs in anterior femoral region and region of stifle, and in anterior pectoral region. Diffuse redness of nasal mucous membrane and conjunctiva. Difficulty in movement. General condition fairly good.
5.2.47	56	13	101.0	Œdematous swelling appeared in region of nostrils and upper lip. Nostrils painful on manipulation. No other change.
6.2.47	56	18	101.0	Nasal mucous membrane still red and swelling of the pectoral region unchanged. Gradual reduction of the other swollen areas. Conjunctiva normal. Movement less difficult. General condition improving.
8.2.47	43	12	100.0	Continued improvement.
13.2.47	48	12	100.2	Animal apparently normal.
14.2.47	48	10	100.0	Animal regarded as recovered.

Horse G

Gelding, age six years.

Purpura first diagnosed on February 10, 1947.

Date	Pulse/ min.	Resp./ min.	Rect. temp.	
11.2.47	70	11	102.5	Slight diffuse œdematous swelling of the whole pectoral region. Nasal mucous membrane and conjunctiva normal. General condition fairly good.
12.2.47	68	16	101.2	Increased swelling of pectoral region. Slight œdematous swelling of anterior femoral region on both sides and of upper lip and nostrils. Nostrils painful on manipulation. General condition unchanged.
13.2.47	88	9	103.6	Continuous nasal discharge, chiefly from right nostril. This discharge was reported as having been at first thick and purulent, but on this occasion and subsequently it was thin, watery, pale yellow and opalescent. Swelling of nostrils now marked, especially over alar cartilages,

13.2.47	88	9	103.6	so that external nares partially obstructed, causing difficulty in breathing. Unilateral œdematous swelling of medial aspect of right thigh and of triceps region in fore leg. Swelling of pectoral region now massive and extended over anterior abdominal region, with its posterior limit well defined and situated just anterior to the preputial orifice. General condition deteriorating.
14.2.47	85	15	104.2	General condition now extremely exhausted. No other changes.
17.2.47	85	13	102.0	General condition improved. No other changes.
18.2.47	94	11	101.5	No change.
19.2.47				Animal died in early hours of morning.

General Discussion of Clinical Data

On the whole, the symptoms observed are fairly typical of purpura hæmorrhagica. Characteristically, there was in every case the appearance of pronounced œdematous swellings, the absence of a consistent fever, and the history of a previous respiratory disease. The veterinary surgeons of the L.M.S. Railway, and those of the Royal Veterinary College concerned in the preparation of this series of papers, were left in no doubt as to the diagnosis.

However, it may be of interest to call attention to a few of the variations encountered. For example, most authorities, e.g. Hutyra *et al.* (1938) and Udall (1943), emphasise the occurrence of a distinct line of demarcation on the limbs between œdematous and normal areas and the presence of bilateral symmetry in the disposition of the swellings. The former characteristic was never conspicuous in any of our cases, but we thought it was to be expected that this symptom would be masked in thick-legged draught horses, such as those encountered in this investigation; possibly for the same reason, we could not confirm the observation stressed by Davenport (1937) that, in the affected limbs, the œdema should mount progressively from the distal extremity. A symmetrical disposition of the œdematous swellings was often observed, but was by no means constant; for example, horse G developed a conspicuous unilateral swelling of the right thigh and shoulder on February 13 (see case record of G), and in horse C, also, there were periods of asymmetry.

The presence of petechiæ on the visible mucous membranes, which seems generally to be regarded as pathognomonic of this disease, was decidedly irregular in the cases reported here. Horse C, it is true, showed nasal petechiæ from the second day, but in G they were always absent, and in F there was only a diffuse redness of the nasal mucosa. According to some authorities, e.g. Editorial (1942), it is even common for petechiæ to extend over any of the mucous membranes of the body, but in none of our cases, either alive or at post-mortem, were hæmorrhages found either in the mouth, eye or vagina.

There are a few additional observations, applicable to all the cases, which now require mention.

Attempts were made to discover the quality and quantity of the urine passed daily. This intention is beset with obvious difficulties, but it was observed that no urine, either collected artificially or seen during micturition, showed any visible abnormality such as discoloration by blood. It was thought, however, that the condition of oliguria was generally present.

The gastro-intestinal tract showed no signs of pronounced dysfunction, such as complete constipation, or diarrhœa. The appetite usually remained surprisingly good.

Three points remain which, because of their relationship to some of the hæmatological and biochemical findings reported later in this series of papers, are thought to merit more detailed discussion.

First, comparison should be made of the recordings of pulse rate with those of rectal temperature in the two more severe cases of C and G. The rectal temperature varied in C from normal to 105.0, and in G from near normal, 101.2, to 104.2. The average temperature is not very high in either case, being 102.3 in C and 102.5 in G. The pulse rate per minute varied between 44 and 103 in C, and between 68 and 94 in G, averaging 71 in C and 81 in G. (The figures given for the normal animal by Miller and Robertson [1937] have been adopted.) It is believed that these figures, from cases C and G, show the average pulse rate to be relatively more in excess of the normal than the average rectal temperature. Udall (1943) confirms this observation directly, and Hutyra *et al.* (1938) support it by implication. Whilst it is open to several possible explanations, it is thought that it could be regarded as suggestive of circulatory embarrassment; the finding by Biggers and Ingram (1949) of anæmia, or of phases of hæmoconcentration, further upholds this interpretation.

Secondly, in the course of repeated venepunctures for collection of blood samples, no gross abnormalities in the blood-clotting process were encountered.

The final point concerns horse C. Consideration of the clinical record of this case leads to the impression that, during the course of the disease, there were three crises, of which the first and last were fairly distinct, although the second was much less definite. The first crisis occurred on February 4 (see case record). It is demonstrated by the fact that, on this day, the œdema, which had been steadily increasing, attained, for the time being, its maximum; it is also shown by the fact that the general condition, which had been daily deteriorating, now reached a state of weakness as serious as at any time during the course of the illness. A second crisis seemed to develop on February 8, but was less obvious than the first; on that day the advance of the œdema was resumed, and during the night the animal was sufficiently weakened to go down. The third crisis, which appeared on February 20, was indicated by a sudden worsening of the general condition, which was the more outstanding when contrasted with the improvement recorded on the previous two examinations. Hæmatological tests, which were done on the blood of this horse after the clinical notes for the day had been taken, show that these crises appear to be synchronous with hæmoconcentration.

The significance of these three points will receive further consideration in the final paper of this series (Biggers *et al.* [1949]).

Summary

1. A general account is given of the epizootology of the outbreak of influenza and purpura in the L.M.S. stables, London, 1946-47. Over 900 cases of influenza occurred; purpura appeared in 10 of these horses, after an average interval of two weeks, and six of these cases were fatal.

2. The material forming the basis of this paper and subsequent papers in this series is listed. Six horses, given the index letters B, C, D, E, F and G, all afflicted with purpura, were examined. Of these, B, C, F and G were examined clinically, and B, C and G also at post-mortem. F recovered. D and E were seen at post-mortem only.

3. The clinical records of horses B, C, F and G are given.

4. The general conclusion is reached that, symptomatologically, the cases examined were typical of purpura hæmorrhagica in its most essential characteristics.

5. Certain atypical features receive comment, principally the absence of a distinct line of demarcation on the limbs between œdematous and normal areas and the scarcity of petechial hæmorrhages.

6. No sign of renal damage was encountered, but a state of oliguria seemed generally to be existent. The gastro-intestinal tract showed no marked dysfunction.

7. The pulse rate was usually considerably accelerated, while the rectal temperature was only moderately increased. It is thought that this could indicate circulatory embarrassment.

8. Numerous venepunctures gave no evidence of gross abnormality in the blood-clotting process.

9. In the case of horse C, crises appeared to develop on at least two occasions, which will be shown in a subsequent paper to coincide with phases of probable hæmoconcentration.

Acknowledgments

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XUM

CLINICAL ARTICLE

OBSERVATIONS ON THE USE OF COD-LIVER OIL

Applied Locally in External Eye Affections, together with the Report of the Treatment of a Mare with Pronounced Corneal Opacity

By O. V. GUNNING, D.V.M., F.R.C.V.S.

An article reprinted from *The British Journal of Ophthalmology* and published in *The Veterinary Record*, May, 1937, is of interest as it records a series of case records of various eye conditions in man treated with cod-liver oil as a local treatment.

The writer is evidently a doctor, practising adjacent to shipbuilding yards where eye injuries are of frequent occurrence.

The cases cited include a very severe burn to the inner half of both right eyelids from a red-hot rivet which adhered to the patient's lids until he reached ground from the top of a 40 ft. ladder. A drop of weak atropine solution was placed in the eye and the burn dressed with a pad of gamgee soaked in ordinary cod-liver oil and covered with oiled silk and a bandage. He had no other treatment except the oil and wiping away any mucus and the preliminary drop of atropine. He returned to work on the fifteenth day. On examination, after two months, the eye looked normal, except that the lids had lost their skin where burnt and also some lashes. Another case recorded was due to a splash of liquid caustic damaging the conjunctiva of the upper lid, the lower half of the cornea and conjunctiva and deeply burning the lower fornix. The case, treated similarly, made a good recovery. Other corneal conditions cited include a very deep linear abrasion about 1 mm. wide, horizontally across two-thirds of the cornea, with ragged edges, and a smaller one less deep below it, caused by a flying piece off head of rivet. Drops of weak atropine and oil were instilled and a pad strapped on. Next day, except for an almost invisible white line in the cornea, there was no sign of any injury. It is stated "the rapid healing in this case surprised us."

The writer, in summing up, states cod-liver oil applied locally seems to promote growth of the natural tissues and to inhibit growth of scar tissue in any case where there is loss of substance. It should be withheld in the early stages of hypopyon ulcer. It is harmless, can be used in conjunction with other necessary treatment, is cheap and easily applied.

In the same issue of *The Veterinary Record* there is a further article on the external use of cod-liver oil by George Dykes, M.R.C.V.S., of Glasgow, in which he discusses the reasons for the curative effect of this oil. He explains that the early workers lent support to the belief that its virtue was centred upon its vitamin content. Experiments, however, were conducted with Halibut liver oil—then of recent introduction. Contrary to expectations, the results were so definitely less successful in regard to the rate of healing that grave doubt was cast upon the tenability of the vitamin theory in local wound treatment. Accordingly, it is assumed that the oil itself is the prime factor in assisting the healing

of ulcers and affected wounds. After going into further details on the mode of action of the oil, he records the five following conclusions:

(1) That in ulcers, which include those of the cornea, and in infected accidental wounds, the local application of cod-liver oil has recommendations which place it above other vegetable and mineral oils which were the subject of test under clinical conditions.

(2) That its vitamin content does not appear to play any appreciable part in assisting the healing of wounds.

(3) That the oil itself is, in the first instance, sedative and protection.

(4) That in the process of decomposition *in situ*, undetermined processes are in operation, but two factors in the main are considered: (a) the production of "active oxygen"; (b) terminal acid products.

(5) That the pack method is indicated in the treatment of wounds.

The above articles prompted the writer to apply this treatment to the following case:

During the war years, actually Sunday morning, January 31, 1943, an urgent message was received to attend a horse which had been rescued at the last moment from a burning stable.

The subject found presented was a bay driving mare, six years old. Her head, face and ears were badly seared, including the eyes, the cornea of which showed a dense opacity. The mare was obviously in acute pain and looking continuously at her near side; the near shoulder was noticed to be coming up in plaques under the skin. Both sides of the body, legs and tail were all singed and she smelt much like a burnt haystack.

The case looked pretty hopeless, especially the eyes, and destruction would have been willingly carried out immediately.

The owner was, however, adamant in his desire to attempt treatment, and tannic acid jelly was therefore liberally applied to the sides of the body and head and all moist parts liberally dusted with sulphanilamide. As the mare continued in pain, before leaving the worst parts were liberally applied with eczema ointment (Willows). From memory, this is a combination of zinc oxide, phenol and cocaine, incorporated in a lanoline base and put up for human use. This treatment may not be conventional, but, in the writer's experience, has been of particular value in relieving pain in burns.

The mare was further given a hypodermic injection of morphine, together with an injection of soluseptasine and the eyes treated with cod-liver oil.

On the following morning the mare looked very dejected and she was given a further injection of soluseptasine. The eyes were badly swollen and were with difficulty injected with atropine and cocaine (which was not available on the previous visit). From this time onwards, the eye received no other treatment but continual applications of cod-liver oil.

On the third day the mare was eating well but doing a lot of sleeping; it was thought that the eyes were paining her.

On the fourth day the eyes were not so swollen and she stopped rubbing them. They were increasingly less swollen on the sixth and eighth days after the injury.

By the eleventh day the left eye was normally open and there was a marked improvement in both eyes.

By the seventeenth day the opacity had completely cleared. At this time the skin of the head had been peeling some time and the skin of the shoulder and sides began to come away in large sheets, the under surface of which was treated with euflavine solution and sulphanilamide.

On the twenty-fourth day the eyes were examined with an ophthalmoscope. This clearly showed up the retina and both eyes looked normal in every way.

By the fourth week the new hairs were growing well on the head, and by the sixth week new islands of hair were noted growing on the back and sides.

Three months after the accident the mare gave birth to a live healthy foal. With the exception of a rest during the suckling period, the mare has been in continuous work since. The mare, examined a few weeks ago in harness, shows no signs of the injury except a copious supply of white hairs over the head and body. The driver, an old-time horseman, questioned about the sight, stated the mare showed no signs of defective vision.

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ABSTRACT

DIFFERENTIAL DIAGNOSIS OF RESPIRATORY DISEASES OF POULTRY*

By ERWIN JUNGHERR

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RESPIRATORY diseases constitute one of the foremost disease problems facing the poultry industry to-day. The average poultryman thinks of respiratory diseases as of varieties of "a common cold." From the scientific standpoint, it is very doubtful that there is such a thing as a "common cold" in either man or animals. Probably more work has been done on the "cold" problem of poultry than of any other domesticated group of animals. This work has primarily served to separate the known from the unknown. In the application of available knowledge, the practising veterinarian should play the same intrinsic rôle as in any other animal disease control programme. To fulfil this mission a basic knowledge is necessary of the symptomatology and gross pathology of the main respiratory entities. Familiarity with the principles of the various laboratory tests will be extremely helpful in the correlation of field and laboratory findings and points the way to effective control measures.

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XUM

Classification

We should develop the topic by emphasising those features which both in the field and in the laboratory permit a diagnosis. There is a list of about nine diagnosable entities showing involvement of the respiratory tract: (1) fungus disease, known as brooder pneumonia or aspergillosis; (2) bacterial diseases, namely chronic fowl cholera and infectious coryza; and (3) virus diseases, namely fowl pox, infectious bronchitis, infectious laryngotracheitis, Newcastle disease, and perhaps fowl paralysis and vitamin A deficiency. Other incompletely defined diseases will be mentioned.

Aspergillosis

Aspergillosis may cause high mortality in brooder chicks and, to a lesser degree, in adult chickens and turkeys. Due to the peculiar structure of the avian respiratory tract having organ pipe-like bronchi which pierce the lung tissue and communicate with the air sacs, birds are structurally predisposed to deep-seated fungus infections. The finding of bluish-green fungal colonies in lung or air sacs on post-mortem examination or the cultural isolation of a member of the *Aspergillus fumigatus* group is diagnostic.

Chronic Fowl Cholera

Chronic fowl cholera is a specific bacterial infection of all kinds of domesticated birds, especially chickens and turkeys. Pheasants are more likely to suffer from the peracute septicemic form. The disease is more prevalent in adult chickens than in young ones and tends to occur in an enzootic form with low continuous mortality. Respiratory tract localisation frequently brings about caseous exudate in the wattles, auditory canals, infraorbital sinuses and air sacs. Fighting among males may hasten the ordinarily slow spread of the disease. Injection of caseous material into rabbits or mice is usually fatal within 12 to 24 hours. This test may be supplemented by demonstrating bi-polar Gram negative rods in the cardiac blood of the test animals, either microscopically or culturally.

Coryza

Infectious coryza is caused by *Hemophilus gallinarum*. The disease occurs mostly in young laying stock, but may affect growing chicks and cause considerable mortality. The spread is usually slow. The most characteristic feature is the development of œdematous or fluctuating swellings in the region of the sinus, eyelids and wattles, accompanied by copious clear viscid discharge from the nostrils. There may be "canker" plaques in the mouth. The diagnostic feature in the field is a rather dramatic response to 1 to 2 per cent. sulphathiazole in the feed for about two days; in the laboratory, of course, diagnosis is obtained by the bacteriologic identification of the causal organism.

Among the virus diseases, fowl pox is the best known. Well-isolated, elevated, greyish-yellow lesions, becoming crusted and confluent, on the glabrous portions of the skin are diagnostic for the dry form. Picking wounds and staphylococcus-induced lesions, or crusts in the skin over the keel bone, may give rise to confusion. In such cases transmission experiments to susceptible birds, or better, histological demonstration of intracytoplasmic inclusion bodies,

should be resorted to. The wet or diphtheritic form causes yellowish, firmly adherent membranes around the base of the tongue and in the upper œsophagus and occasionally in the larynx. Removal of such membranes leaves a bleeding underlying surface. The mortality may be high. Prompt diagnosis is important for instituting prophylactic and emergency vaccination.

Laryngotracheitis

Infectious laryngotracheitis is the most severe respiratory disease in adults from the standpoint of mortality and loss in egg production. However, the disease may occur in growing birds. Rapidly developing morbidity is accompanied by severe gasping, extension of head and neck, and other evidence of acute respiratory embarrassment, which frequently leads to sudden death by suffocation. Coughing is often accompanied by "blood spitting," in the language of the poultryman. Less severe cases show serous conjunctivitis and rhinitis. Loss in egg production is almost complete and lasts from four to eight weeks. Characteristic post-mortem lesions consist of hæmorrhagic-mucoid exudate in the trachea, quickly turning into a yellowish membraneous lining. The laryngeal opening often contains an almost obstructive plug of yellowish exudate. Similar exudate, but less adherent than that of diphtheritic fowl pox, may be present in the oral cavity. Typical hæmorrhagic or diphtheritic tracheitis is diagnostic. Atypical cases can be diagnosed by (a) showing resistance to specific cloacal vaccination of recovered birds; and (b) transmission experiments to either susceptible chickens or chorioallantoic membranes of embryonating chicken eggs. Both of the latter tests can be effectively supplemented by histological demonstration of specific intranuclear inclusion bodies in the experimental chickens or extrafœtal membranes. Prompt diagnosis is of extreme importance for ascertaining the specific immunity and probable carrier status of the flock, and for applying prophylactic and emergency vaccination.

Infectious bronchitis of chicks and chickens is probably the most widespread virus-induced respiratory disease. In baby chicks the disease may cause high mortality; in growing birds, marked impairment of growth; and in laying birds, a 50 to 70 per cent. reduction in egg production for several months. Eggshell quality is poor throughout the period of decreased egg production, it remains so for much longer than the respiratory course of the disease of about two to three weeks, while hatch-ability is the last physiological expression to return to normal. Symptoms develop after an incubation period of less than 24 hours and comprise all the signs of a catarrhal rhinitis and tracheitis. Coughing, sneezing and, later, moist tracheal rales are common. When opened, the upper or lower respiratory tract shows excess sero-mucoid exudate, with the bronchi and the air sacs occasionally showing small amounts of caseous material. On account of the indefiniteness of the signs and symptoms, an accurate diagnosis can be made only by virus isolation in active cases or by serum neutralisation tests in recovered birds. There is no treatment except good nursing. Brooder chicks from bronchitis-immune stock have been shown to carry passive immune bodies for about four weeks and are thereby presumably protected. Live virus inoculation of growing birds six to twelve weeks of age, and preferably still held in heated brooder houses,

has been found a practicable measure of immunising the laying flock in a number of New England States.

Newcastle Disease

Newcastle disease is the most recently recognised respiratory virus disease of poultry. On the East Coast its existence has been known for less than three years. Due to its pandemic occurrence in foreign countries associated with nearly 100 per cent. mortality in adult birds, the disease has received wide publicity in this country. In chicks under four weeks of age the mortality may reach 75 per cent.; in growing birds the mortality may be quite severe, particularly if the disease is complicated by coccidiosis, etc.; in laying birds there is a precipitate drop in egg production down to zero with recovery in three to four weeks. The few eggs laid are chalky white, soft-shelled and malformed. Individual symptoms are a relatively mild upper respiratory catarrh, which in young birds may be followed by nervous symptoms. The nervous manifestations are suggestive of either fowl paralysis or epidemic tremor at certain stages; or they may bring about characteristic twisting of the head and neck, aptly termed "down benders" or "star gazers." On post-mortem examination, cloudiness or yellowishness of the pulmonary and abdominal air sacs is the most suggestive finding. Egg follicles in production are irregular and soft, likely to spill the contents into the abdominal cavity. A specific diagnosis can be made by virus isolation in embryonating eggs. This succeeds only with active cases. Recent or past infection can be shown by serum neutralisation and hæmagglutination inhibition tests. Unfortunately, these tests do not indicate the time of infection, unless a rising titre is shown by serial tests. Thus, a bird infected two years ago reacts serologically more or less like a bird infected two weeks ago.

The question of avian immune carriers has not been settled. Three months is the longest period reported. The virus is unusually hardy, as shown by its persistence, under laboratory conditions, on feed bags for several weeks. Eggs and chicken mites may contain the virus during the active phase of the disease.

Other Diseases

Fowl paralysis is considered to be due to a tumour-producing or oncogenic virus. If it affects the vagus nerve, respiratory symptoms may be present. But such cases are definitely sporadic and usually associated with visceral or nervous expression of the disease.

Vitamin A deficiency is rare at the present time. Secondary bacterial infection of the sinuses may cause so-called "nutritional roup." Early cases show caseous triangular plugs in the conjunctival sac and prominent whitish glandular follicles in the œsophagus. A specific diagnosis can be made by histological examination of the nasal passages.

In the listing of causal agents of avian respiratory diseases no mention was made of diseases caused by agents of the lympho-granuloma venerum group. However, even here we find representatives. Ornithosis has been found in pigeons, ducks and chickens and may become of greater importance. Turkey sinusitis followed by air sac infection may be caused by such a similar agent, according to recent work in our laboratory.

So far, incompletely studied respiratory diseases and mixed infections complicate the picture. Among the first group must be mentioned the chronic form of coryza, shown by Nelson to be caused by coccobacilliform bodies, and the chronic, presumably viral, respiratory disease described by Delaplane. The latter condition resembles that observed by Komarov in Palestine, especially in its transmissibility to turkeys.

Mixed infections are of ordinary occurrence, but seldom recognised on account of incomplete analysis. Thus the combination of bronchitis and Newcastle disease, especially as past infections, is common. Newcastle disease has been found in association with fowl cholera, fowl paralysis and aspergillosis; laryngotracheitis with fowl pox. Nervous symptoms in combination with unidentified "sniffles" were found to be due to vitamin E deficiency (encephalomalacia). There is no end of possible combinations. Eggs transferred passive immunity to Newcastle disease and bronchitis often upsets epizootiologic reasoning. The occurrence of asymptomatic bronchitis and Newcastle disease, except for drop in egg production, is confusing. Analysis of instructive cases by all available methods is the only way of shedding further light upon these questions.

It cannot be emphasised too strongly that the results obtained by the laboratory technician are always more satisfactory if he has had the active co-operation of the veterinarian in the field.

REVIEW

The Milk Marketing Board. By R. A. PEPPERALL; 1948. Price: 4s. 6d. (Obtainable only from the Librarian, M.M.B., Thames Ditton, Surrey.)

The Milk Marketing Board is now such an integral and established feature of the milk selling business in this country that one needs almost an effort of memory to recall the perilous economics of milk production that existed some fifteen to twenty years ago. It was from the grim necessity of those days that the Milk Marketing Board came into being—an organisation charged with rescuing the milk producers of England and Wales from the bankruptcy which threatened them and invested with the necessary statutory authority for the task. "The M.M.B. is a 'body corporate,' comprising the whole of the dairy farmers of England and Wales, which has been entrusted by Parliament with the Statutory powers necessary to carry out the task of regulating, on a collective basis, the sale of their milk." The Board thus ranks as one of the largest producer co-operative organisations in the world, "with an ever-increasing annual turnover which in the year ending 30th September, 1947, exceeded £136 million, representing the sale of 1,244 million gallons of milk." This book by Mr. R. A. Pepperall, now secretary of the Board, tells simply and clearly, and without obtrusion of wearisome figures and statistics, the history of the Board during the fourteen years of its existence up to 1948. Within the compass of 106 pages he outlines the evolutionary development of the Board, starting from the early

period of administrative problems and political difficulties, through the period of surmounting these to a time when the success of the Board was firmly established and its functioning so highly efficient as to be the envy of most of the other dairying countries of the world; and so finally to the year 1939, and onwards, when, with the outbreak of war, the Board came under the direction of the Ministry of Food in regard to the actual marketing of milk.

Mr. Pepperall describes the varied activities and interests which the Board has developed in its comparatively short life. The story has for all of us, consumers of milk as we are who take but little heed of the problems connected with its production and distribution, a personal interest and conveys much that will be enlightening to the general public. The veterinary reader will find authoritative information on some of the aspects of milk production that directly concern the work of his profession, e.g. the Board's part in the campaign for improved standards in the handling of milk, in this connection its introduction of the "Accredited Scheme" shortly after its (the Board's) formation in 1933, but especially the new avenues into which the Board has recently turned its resources, such as its assumption of responsibility for the conduct of National Milk Records and the creation of a Bureau of Milk Records, its participation in livestock improvement and responsibility for the development of a country-wide artificial insemination service for the smaller herdowner, and, finally, its interest in the raising of standards in cattle nutrition, exemplified by exploration in 1947 and 1948 of the practicability of grass drying on a communal basis.

The information about the M.M.B. set forth in this book comes opportunely to-day for another and more particular reason, namely in view of the great deal of uninformed controversy which continues to take place following the recommendations of the Lucas Committee on agricultural marketing; in so far as the affairs of the Board are concerned, a perusal of the book's contents should correct any lack of knowledge on the part of the discursists.

This book will be welcomed by members of the veterinary profession for the panorama it sketches of an industry with which we are vitally concerned. We believe that one of the surest ways of increasing the production efficiency of the dairy cattle of this country beyond its present limit is by the more effective control of several major diseases affecting the various herds—an aspect, unfortunately, about which Mr. Pepperall has little to say. Apart from this minor criticism, Mr. Pepperall tells a fine story of co-operative pioneering by producers, of organisation and planning which brought confidence and stability to an insecure industry, and of dynamic progression towards ever greater efficiency, not only in the marketing of milk, but also at almost every stage in the production of that commodity.

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